Synthesis and structure—activity relationships of cyclopropane-containing analogs of pharmacologically active compounds*

I. A. Novakov,[a] A. S. Babushkin,[a] A. S. Yablokov,[a] M. B. Nawrozkij,[a] O. V. Vostrikova,[a] D. S. Shejkin,[a] A. S. Mkrtchyan,[a] and K. V. Balakin[b,c]*

[a]*Volgograd State Technical University, 28 prosp. im. Lenina, 400131 Volgograd, Russian Federation. E-mail: maxim.nawrozkij@gmail.com*
[b]*Kazan Federal University, Education and Research Center of Pharmacy, 18 ul. Kremlevskaya, 420008 Kazan, Russian Federation*
[c]*I. M. Sechenov First Moscow State Medical University of the Ministry of Healthcare of the Russian Federation (Sechenov University), Build. 2, 8 ul. Trubetskaya, 119991 Moscow, Russian Federation*

The review summarizes information on cyclopropane as an independent pharmacophore group and as a fragment for modification of pharmacological activity level of medicines used in practice. The advantages of a cyclopropane fragment over its bioisosteres are that, on the one hand, this fragment imposes conformational rigidity on the molecules of physiologically active compounds and, on the other hand, the replacement of acyclic terminal and "linker" groups with a cyclopropane fragment increases the metabolic stability of the target structures and extends the scope of their therapeutic action.

Key words: cyclopropanes, pyrimidines, cycloaddition, heterocyclization.

Introduction

Compounds containing a cyclopropane fragment are of considerable interest for both organic chemists and biochemists. The three-membered saturated carbocycle is a structural element with a wide synthetic potential due to the high strain energy (~ 27.5 kcal mol^{-1}) of an unusual type of carbon—carbon bonds known as "banana" bonds. The nature of these bonds is regarded as being intermediate between σ- and π-bonds, due to which cyclopropane derivatives can be involved into various ring opening and ring expansion reactions, as well as into cycloaddition reactions.[1—4] From the point of view of medical use, it should be noted that eight of the 200 best-selling pharmaceuticals in the US as of 2012 (Fig. 1) are compounds containing a cyclopropane fragment. [5—12]

From the given examples, it is seen that cyclopropane functional derivatives possess a wide range of biological activity. Thus, they inhibit enzymatic activity (monoamine oxidases,[13,14] DNA gyrase,[15] aldehyde dehydrogenase,[16—18] amino acid decarboxylase,[19] carboxypeptidase,[20—22] histidine carboxylase,[23] tyrosine aminotransferase,[24,25] spermine/spermidine-N^1-acetyltransferase (SSAT),[26] DNA polymerases of herpes simplex virus (HSV)[27] and HIV,[28—30] acyl coenzyme A dehydrogenase,[31] *etc*.), exhibit receptor activity (acetylcholine receptors,[32,33] estrogen receptors,[34,35] thyroid hormone receptors,[36] γ-aminobutyric acid (GABA) receptors,[37] ethylene receptors,[38,39] *etc*.), as well as play the role of inductors of cell apoptosis of malignant neoplastic cells.[40]

A cyclopropane fragment can either play the role of a structural element of the pharmacophore or participate in the "decoration" of the pharmacophore group as a modulator of the corresponding type of biological activity. In this connection, it is necessary to focus on the biological activity of cyclopropane itself (obtained by debromination of 1,3-dibromopropane with zinc[41]), which is used in clinical practice for inhalation anesthesia.[42] Its main advantages are the absence of irritating action on the respiratory tract and rapid recovery from anesthesia. Among the simplest cyclopropane functional derivatives, one can name cyclopropane-1,1-diol (a stable hydrate of cyclopropanone) (**1**) possessing inhibitory activity against yeast aldehyde dehydrogenase (ALDH).[16,17] Cytoplasmic and mitochondrial aldehyde dehydrogenases found in beef liver are also inactivated by cyclopropanone hydrate **1** as a result of covalent modification of the fragment of heme composing the coenzyme[18] (Scheme 1).

trans-2-Phenylcyclopropylamine (tranylcypromine, transamin) (**2**) is the first commercially available agent having a cyclopropane fragment in the molecule. The first

* Dedicated to Academician of the Russian Academy of Sciences I. P. Beletskaya.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 0395—0418, March, 2018.
1066-5285/18/6703-0395